

Neurocritical Care

Development and validation of a nomogram for predicting bacterial meningitis in postoperative neurosurgical patients

--Manuscript Draft--

Manuscript Number:	NECA-D-21-00546R2
Full Title:	Development and validation of a nomogram for predicting bacterial meningitis in postoperative neurosurgical patients
Article Type:	Take Notice: Technology
Keywords:	neurosurgical patients; bacterial meningitis; Predicting; Nomogram
Abstract:	<p>Background</p> <p>The purpose of this analysis was to create a nomogram for predicting postneurosurgical bacterial meningitis.</p> <p>Method</p> <p>A retrospective study of patients underwent a neurosurgical procedure and suspected postneurosurgical bacterial meningitis at Nanfang Hospital, Southern medical University from 15 January 2014 to 15 January 2020. The model was internally validated using bootstrap resampling. Subsequently, the model was validated externally a separate cohort of patients (N=63) from 16 January 2020 to 16 January 2021. The concordance index and calibration curve was used to assess the discrimination and calibration of the model. Decision analysis curve was used to evaluate the clinical performance.</p> <p>Results</p> <p>Independent factors derived from multivariable analysis of the primary cohort to predict intracranial infection were CSF WBC count (cerebrospinal fluid white blood cell count), CSF lactate concentration, and CSF glucose concentration were all assembled into a nomogram to predict intracranial infection. The calibration curve for the probability of intracranial infection showed that the nomogram-based predictions were in good agreement with actual observations. The C-index (concordance index) of nomogram model for predicting risk of intracranial infection was 0.933 (compared with only CSF glucose, CSF lactate, CSF WBC counts, $P < 0.001$, DeLong's test). The results were confirmed in the validation cohort (C-index =0.908). Decision analysis curve demonstrated that the nomogram is valuable tool.</p> <p>Conclusion</p> <p>The proposed nomogram may be served as an effective tool for predicting postneurosurgical bacterial meningitis.</p>
Additional Information:	
Question	Response

Dear Editor and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Development and validation of a nomogram for predicting bacterial meningitis in postoperative neurosurgical patients". Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Page 6: For primary outcome criteria: please explain what is the difference between (1) CSF bacterial culture and (2) CSF cultures? Furthermore, the gold standard for meningitis diagnosis appears to include the actual independent variables used in the model-building to predict this outcome. Please explain as this is concerning. Please show data on how many patients met each of these criteria 1, 2 and 3.

Responses: Cerebrospinal fluid culture is the same as cerebrospinal fluid bacterial culture.

Diagnosis of PNBM should not be made on a single abnormal result, because a single test result may not be reliable in the early phase of the disease. It may be more accurate to predict the PNBM with multiple results.

Through nomogram, the sensitivity, specificity, positive predictive value and negative predictive value were improved. Accurate and rapid diagnosis of bacterial meningitis is very important in neurosurgery, because the result of infection will depend on early and specific antibiotic treatment.

Number of patients meeting the diagnostic criteria: (1) 188 (2) 32 (3) 85

Can the authors explain why they used backward selection for their regression model building? There are several concerns with stepwise regression methods, and as per the STROBE guidelines (PMID: 18313558) confounders selected for inclusion within models should be fully explained.

Responses: The stepdown approach was suggested by Harrell, as the step-down method(backward stepwise variable selection) is preferred for the following reasons.

1. It usually performs better than forward stepwise methods, especially when collinearity is present.
2. It makes one examine a full model fit, which is the only fit providing accurate standard errors, error mean square, and P-values.
3. The method of Lawless and Singhal allows extremely efficient step-down modeling using Wald statistics, in the context of any fit from least squares or maximum likelihood. This method requires passing through the data matrix only to get the initial full fit.

- Unfortunately, the reference quoted by the authors does not support backward

stepwise elimination methods. This paper (PMID: 12483768) concentrated only on the predictive accuracy of the model in prognostic studies and did not consider statistical inference, i.e., confidence interval coverage and estimation of effects for individual variables.

Responses: This quoted reference only suggest that application of backwards elimination at the 0.05 level is inappropriate when we know from prior knowledge that all the candidate predictors are influential to some degree. Actually, for a specific nomogram, the discrimination and calibration is important than confidence interval coverage and estimation of effects for individual variables.

"Backward elimination was used to identify the risk factor for developing the nomogram." – these independent variables are not risk factors for developing meningitis, they are more appropriately associated with the development of meningitis. Consider "Backward elimination was used to identify variables associated with the development of meningitis".

Formatted: Font color: Red

Responses: Thank you for your comments, which have been modified accordingly.

Please provide data on the percentage of missing data % for each variable? Please adhere to best practices as per Equator Network for observational studies (see PMID: 18313558 for the STROBE guidelines).

Responses: Thanks to the referee's comment Percentage missing : multinuclear percentage, 2.8% CSF lactate concentration, 8.1% CSF Cl⁻, 2.9%, CSF glucose 3%, CSF ADA 2.6%, CSF total protein 2.9%, blood glucose 3.6%, procalcitonin 28.4%, and the CSF/Blood glucose ratio 5.2%

STROBE checklist has been completed. See supplementary materials for details

As per Equator Network for predictive studies, I strongly suggest the authors complete the TRIPOD checklist with the next revision to ensure the transparent reporting of their predictive models (PMID: 25569120).

TRIPOD checklist has been completed. See supplementary materials for details

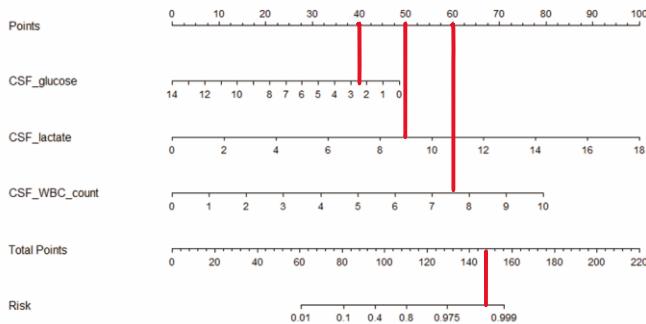
Sample size: "We considered about 5 significant clinical factors in developing model. This would have required us to recruit a minimum of 50 (5×10) participants who had event prediction for the development of infection". This statement is unclear. You needed at least 50 patients to have meningitis (the event) out of your total cohort to allow 5 independent variables into your model. Please reword. Also, be specific with terminology- "We considered about 5 significant clinical factors in developing model". If only 5 were considered, then reword as follows "We considered about 5 significant clinical factors in developing model." However, it appears more than 5 variables were considered when reviewing table 2. Please

explain.

Responses: Thank you for your opinion, I have correspondingly modified. In the study design, we expect that five variables can be included in the model, in fact, eventually only 3 variables are included in the final model.

Nomogram interpretation: Please provide an example (perhaps in the Figure legend) of how a reader should use the nomogram to predict the risk of infection.

Responses: Thanks to the referee's comment



Eg: WBC counts: $7.5 \times 10^9/L$ CSF glucose: 2.5mmol/L CSF lactate concentration 9mmol/L

Total point : 150 points (40+50+60)

Risk :0.993

- The authors state the nomogram has been explained in the discussion, but I can find no further edits to address my comment. The discussion focuses on how the nomogram is constructed and I would argue that most of these results belong in the Results section. The discussion does not compare the current study to other studies, strengths or limitations. Please revise the discussion to a standard format.

Responses: I have made the following changes in the discussion.

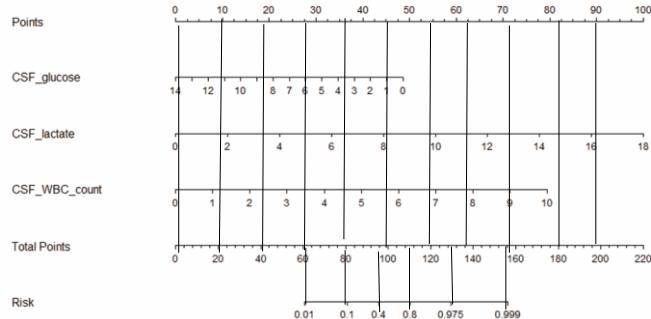
Although nomogram has many advantages, it also has some limitations. Because there are many missing variables in the validation database, on the basis of ensuring the efficiency of the model, we use as few variable parameters as possible to enter the model. Retrospective studies have limitations and specific risk of bias, so prospective cohort was used for internal validation to reduce these bias. In this study, only a nomogram based on single center cases is established, and the generalization of nomogram to other cohorts with similar characteristics still needs to be verified. Our findings have yet to be confirmed by other independent studies. Whether the model predicts BM in the special case of pnbm rather than in other cases remains to be solved. This study

is a single center study, and the universality of risk score to other populations still needs to be verified.

In addition, the bootstrap program that estimates over optimism is based on the developed risk score, which does not include the model selection step. In this case, there may be a large deviation from the overly optimistic estimate.

- A suggestion to help the reader interpret the nomogram might be "Draw an upward vertical line to the "Points" bar to calculate points for each variable. Based on the sum, draw a downward vertical line from the "Total Points" line to calculate?"

Responses: Thanks to the referee's comment



- Please also explain how to use this nomogram in the clinical context, i.e. how does the total points and risk in the nomogram assist in informed decision-making? With the addition of the new 'Outcome' paragraph in the Results section, it does appear that the nomogram and risk assessment has been used to consider the duration of antibiotics. What is the risk cut-off used to stop antibiotics? This question feeds into a comment I previously made in my last review: I suspect the majority of centres and clinicians would opt to start antibiotics while awaiting CSF results due to the high mortality associated with meningitis, so the utility of a nomogram like this will be to rule out, rather than rule in, meningitis to facilitate either early discontinuation of antibiotics. Considering the point above, please consider how the nomogram can help to rule out meningitis, rather than rule in this infection.

Responses: Thanks to the referee's comment

So far, there is still no stopping standard of antibiotics for pnbm. In the context of Neurosurgery, individual prediction of meningitis remains a challenge. In the past, the duration of our antibiotic treatment was mainly based on the recommendations of routine guidelines for meningitis, rather than evidence. When there are no pathogenic results, the duration of antibiotic treatment is often difficult. Since the nomogram chart was developed, when risk < 0.05, we

believe that the risk of meningitis is a small probability event. Therefore, according to risk = 0.05, as the risk limit for stopping the use of antibiotics, the duration of antibiotics is shortened.

Please explain the new results under the heading "Outcome" in the methods section. Please also explain/hypothesize in the discussion section how the authors interpret the new results showing that the nomogram data helps to reduce the treatment failure rate at their institution. How is treatment failure defined?

Responses: Thanks to the referee's comment,

Treatment failure means the patient dies

Since PNBM is a very serious disease, early diagnosis and treatment is very important, which is directly related to the treatment effect of the patient. Based on this Nomogram, it would be advisable to initiate treatment as soon as possible to prevent and treat intracranial infection, thereby reducing the mortality and treatment failure

When revising the discussion and conclusions, mention should be made that prior to clinical application in other institutions, this nomogram should be externally validated in a cohort with similar characteristics as the cohort to which the nomogram will be applied.

Responses: This study only established a Nomogram based on a single center case, generalizability of the nomogram to other cohort with similar characteristics still needs to be validated

Ongoing grammatical concerns- a further revision will improve clarity, flow and interpretability.

Responses: Clarity, flow and interpretability have been improved

Reviewer #2: Thanks for addressing the revisions. I could not find the revision made to the draft to add neuroimaging as mentioned in the revisions synopsis.

Responses: Thanks to the referee's comment,

We usually have to go through CT scanning 24 hours and 72 hours after operation, mainly to check whether there is bleeding, hydrocephalus, tumor resection, peripheral brain edema, intracranial effusion and gas accumulation in the operation area, which has no obvious specificity compared with the imaging examination of meningitis for patients in the early stage after neurosurgery. For the patients with negative cerebrospinal fluid culture, MR (T1, T2, DWI) scanning was performed for these patients with suspected postoperative intracranial infection, and some possible evidences were found, such as thrombosis of drainage venous sinus, infarction, hydrocephalus and epidural empyema, which may develop into subdural empyema,

In order to determine the entrance of infection into the central nervous system, high-resolution thin-layer computed tomography with bone window will be an acceptable imaging method. In most centers, neuroimaging is routinely performed as part of the initial examination of

suspected PNM and other post neurosurgical infections. It is unclear whether all patients suspected of infection after neurosurgery need this routine general imaging.

原信：

Dear Dr Qi,

We found your revised manuscript to be improved however there are persistent concerns that need to be addressed.

They are enumerated in the reviewers' comments below.

When preparing your revised manuscript, please carefully consider the reviewer comments and submit a list of point-by-point responses to the comments.

Your list of responses should be uploaded as a separate file in addition to your revised manuscript.

When uploading your revised files, please make sure only to submit your editable source files (e.g., Word, txt).

When submitting your revised manuscript please upload 2 files, one of the original submission with the changes indicated (track changes) and a second of the final text of the revised version.

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<https://www.editorialmanager.com/neca/>

Your username is: *****

If you forgot your password, you can click the 'Send Login Details' link on the EM Login page.

We look forward to receiving your revised manuscript.

With kind regards,

Michael Diringer
Editor-in-Chief

Neurocritical Care

COMMENTS FOR THE AUTHOR:

Please address the following major concerns before reconsideration.

Reviewer #1: Thanks for addressing some of my prior questions. The following concerns either remain or arose after reading the revised manuscript:

Page 6: For primary outcome criteria: please explain what is the difference between (1) CSF bacterial culture and (2) CSF cultures? Furthermore, the gold standard for meningitis diagnosis appears to include the actual independent variables used in the model-building to predict this outcome. Please explain as this is concerning. Please show data on how many patients met each of these criteria 1, 2 and 3.

Can the authors explain why they used backward selection for their regression model building? There are several concerns with stepwise regression methods, and as per the STROBE guidelines (PMID: 18313558) confounders selected for inclusion within models should be fully explained.

- Unfortunately, the reference quoted by the authors does not support backward stepwise elimination methods. This paper (PMID: 12483768) concentrated only on the predictive accuracy of the model in prognostic studies and did not consider statistical inference, i.e., confidence interval coverage and estimation of effects for individual variables.

"Backward elimination was used to identify the risk factor for developing the nomogram." - these independent variables are not risk factors for developing meningitis, they are more appropriately associated with the development of meningitis. Consider "Backward elimination was used to identify variables associated with the development of meningitis".

Please provide data on the percentage of missing data % for each variable? Please adhere to best practices as per Equator Network for observational studies (see PMID: 18313558 for the STROBE guidelines).

As per Equator Network for predictive studies, I strongly suggest the authors complete the TRIPOD checklist with the next revision to ensure the transparent reporting of their predictive models (PMID: 25569120).

Sample size: "We considered about 5 significant clinical factors in developing

model. This would have required us to recruit a minimum of 50 (5×10) participants who had event prediction for the development of infection". This statement is unclear. You needed at least 50 patients to have meningitis (the event) out of your total cohort to allow 5 independent variables into your model. Please reword. Also, be specific with terminology- "We considered about 5 significant clinical factors in developing model". If only 5 were considered, then reword as follows "We considered about 5 significant clinical factors in developing model." However, it appears more than 5 variables were considered when reviewing table 2. Please explain.

Nomogram interpretation: Please provide an example (perhaps in the Figure legend) of how a reader should use the nomogram to predict the risk of infection.

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- A suggestion to help the reader interpret the nomogram might be "Draw an upward vertical line to the "Points" bar to calculate points for each variable. Based on the sum, draw a downward vertical line from the "Total Points" line to calculate.....?"

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Reviewer #2: Thanks for addressing the revisions. I could not find the revision made to the draft to add neuroimaging as mentioned in the revisions synopsis.

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Development and validation of a nomogram for predicting bacterial meningitis in postoperative neurosurgical patients

Authors:

Qiang Wu^{1,2}, MD; Yun Bao¹, MD, PhD; Haorun Huang¹, MD; Bing-Hui Qiu¹, MD; An Zhang¹, MD; Ming Jin³, MD; Yi-Ping Mo¹, MD; Ya-Wei Liu¹, PhD; Song-Tao Qi¹, MD, PhD; Fen Mei¹, PhD

Affiliations:

¹Department of Neurosurgery, Nanfang Hospital, Southern Medical University, Guangzhou, China

²Department of Neurosurgery, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region, China

³ Department of Gastroenterology, Shenzhen Hospital, Southern Medical University, Shenzhen, China

Qiang Wu, Yun Bao and Binghui Qiu contributed equally to this manuscript.

Corresponding Author:

Songtao Qi, MD, PhD and Fen Mei, PhD, Department of Neurosurgery, NanFang Hospital, Southern Medical University, Guangzhou Dadao Bei Street 1838#, Guangzhou, China

Tel/Fax: +86-20-61641801

E-mails:qisongtaonfy@126.com (Qi), meifen813@126.com(Mei)

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Number of Tables and Figures:4 Tables and 4 Figures

Details Page:

- 1) We confirm that the manuscript complies with all instructions to authors
- 2) We confirm that authorship requirements have been met and the final manuscript was approved by all authors
- 3) We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal
- 4) The entire study was conducted after obtaining ethical approval and informed patient consent and following ethical guidelines
- 5) The authors report no conflicts of interest
- 6) Authors' contributions:

Qiang Wu, Yun Bao, Binghui Qiu performed primary data analysis and wrote the manuscript. Qiang Wu, An Zhang, Haorun Huang, Ming Jin and Yi-Ping are responsible for the collection of date. Ya-Wei Liu and Yun Bao performed statistical analysis of the data. Songtao Qi, Fen Mei designed and supervised the study. All authors edited and approved the final manuscript.

Abstract

Background: The purpose of this analysis was to create a nomogram for predicting postneurosurgical bacterial meningitis.

Method: A retrospective study of patients underwent neurosurgical operation and clinically suspected postneurosurgical bacterial meningitis admitted to neurosurgical intensive care unit of Nanfang Hospital, Southern medical University from 15 January 2014 to 15 January 2020. Firstly, the model was internally validated using bootstrap resampling. Subsequently, it was externally validated in a separate cohort of patients (N=63) from 16 January 2020 to 16 January 2021. The concordance index and calibration curve was used to assess the discrimination and calibration of the model. Decision analysis curve was used to evaluate the clinical performance.

Results: Independent factors derived from multivariable analysis of the primary cohort to predict intracranial infection were CSF WBC count (cerebrospinal fluid white blood cell count), CSF lactate concentration, and CSF glucose concentration. They were all assembled into a nomogram to predict intracranial infection. The calibration curve for predicting the probability of intracranial infection showed that the nomogram-based predictions were in good agreement with actual observations. The C-index (concordance index) of nomogram model for risk prediction of intracranial infection was 0.933 (compared with only CSF glucose, CSF lactate, CSF WBC counts, $P < 0.001$, DeLong's test). The results were confirmed in the validation cohort (C-index =0.908). Decision analysis curve demonstrated that the nomogram is a valuable tool.

Conclusion: The proposed nomogram may be served as an effective tool for predicting post-neurosurgical bacterial meningitis.

Trial registration: Medical Ethics Committee of Nanfang Hospital(Seal), NFEC-2018-050 ,

Registered 15 May 2018, <http://www.nfyy.com/aboutus/zzjg/kyjg/yxllwyh/>

Key Words:

neurosurgical patients; bacterial meningitis; predicting ; nomogram

Introduction

Postneurosurgical bacterial meningitis (PNBM) in neurosurgical patients is a common and serious postoperative complication that threatens patients' lives after neurosurgery¹⁻³, with a mortality of 20 to 50%⁴⁻⁷. Furthermore, survivors of bacterial meningitis have a high risk of cognitive impairment or other neurological deficits⁸. The most common causes of bacterial meningitis are: craniotomy for head trauma, brain tumor or intracranial hemorrhage, placement of external ventricular device, placement of ventriculoperitoneal shunt and ventriculostomy⁹. Patients usually present with fever, vomiting, meningeal irritation, and altered consciousness^{6, 10, 11}. PNBM requires immediate medical treatment. Early treatment with antibiotics reduces mortality in patients with PNBM, and therefore, rapid diagnosis is necessary¹²⁻¹⁴. The early diagnosis of PNBM is often difficult^{11, 13, 15}. Cerebrospinal fluid can be tested for the diagnosis of PNBM¹⁵. The CSF sample is examined for white blood cell count, red blood cell count, protein content, glucose level and bacterial culture. Diagnosis of PNBM should not be made on a single abnormal result, because a single test result may not be reliable in the early phase of the disease¹⁶. It may be more accurate to predict the PNBM with multiple results. The present study was performed to evaluate the prediction effect of the nomogram for predicting PNBM.

Methods

Study Population and Database

A retrospective observational study was conducted. The primary cohort comprised 380 postoperative neurosurgical patients, aged 16 to 77 years old from 15 January 2014 to 15 January

2020, in Nanfang Hospital, Southern Medical University. From 16 January 2020 to 16 January 2021, an independent cohort of postoperative neurosurgical patients (N=63) was prospectively enrolled at the same institution for validation. Both the primary and independent cohort used the same inclusion and exclusion criteria. All participants had given informed consent for this specific study.

Samples of CSF were collected from postoperative neurosurgical patients with suspected bacterial meningitis to develop the nomogram for early prediction of PNBM. Patients had at least one clinical manifestation of bacterial meningitis including fever (temperature \geq 38.5 °C), vomiting, meningeal irritation and altered consciousness. The values of CSF and blood samples were collected during first 8h after the clinical manifestation of bacterial meningitis appeared. CSF analysis included: gram stain and culture, white and red blood cell counts, multinuclear percentage, as well as protein concentration, glucose concentration, Cl⁻, adenosine deaminase (ADA), lactate concentration and the CSF/Blood glucose ratio. Blood analysis included: glucose, procalcitonin (PCT) and C-reactive protein (CRP). Clinical parameters examined included: age, sex, types of surgical procedure.

Primary End Point

The primary end point was the diagnosis of bacterial meningitis according to Practice Guidelines for the Management of Bacterial Meningitis⁹. PNBM confirmed on accurate diagnostic criteria which is (1) CSF second-generation sequencing were positive, (2) CSF Gram stain and cultures were positive, (3) a. CSF WBC count \geq 1000/ μ L and the WBC count of CSF increased in the

second time; b. CSF below 2.5 mmol/L or a ratio of CSF to blood glucose < 0.4.

Sample Size and Missing Data

We had used the rule of thumb recommended by Peduzzi¹⁷ and Harrell¹⁸, events per variable (EPV) being 10 or greater under this circumstance. We considered about 5 significant clinical factors in developing model. This would have required us to recruit at least 50 patients to have meningitis (the event) out of the total cohort to allow 5 independent variables into the model.

The percentage of deletions in our study was: multinuclear percentage, 2.8% CSF lactate concentration, 8.1% CSF Cl⁻, 2.9%,CSF glucose 3%, CSF ADA2.6%, CSF total protein 2.9%, blood glucose 3.6% , procalcitonin 28.4%, and the CSF/Blood glucose ratio5.2%

For missing data in this study, we assumed missing data occurred at random depending on the clinical variables and conducted multiple imputations. The fully conditional specification (FCS) regression method with 5 imputations was used to impute continuous variables. All analyses were performed based on imputed complete cases.

Statistical analysis:

Comparisons between normally distributed continuous variables, expressed as mean ± SD, were performed using two sample t-test. Non-normally distributed continuous variables, presented as median and interquartile range, were analyzed using Wilcoxon rank-sum tests. For categorical data, expressed as percentages, the Pearson chi-square or Fisher exact tests were used, as appropriate. We used multiple imputation to impute missing values for multinuclear percentage, CSF lactate concentration, CSF Cl⁻ , CSF glucose, CSF ADA, CSF total protein, blood glucose, procalcitonin, and the CSF/Blood glucose ratio which were used in the main analyses. We carried

out five imputations. Univariable and multivariable analyses were conducted to develop the nomogram. Candidate predictors that were significant at $P<0.01$ in univariable analysis and were of biological interest or clinical importance were considered for multivariable regression. Backward elimination was used to identify the variables associated with the development of meningitis . The coefficients for each variables were estimated in the five imputed datasets. Besides, Rubin's rule was used to combine the results across the imputed datasets. The interaction of predictors' clinical significance was also examined.

The predictive accuracy of the nomogram was assessed by both discrimination measured by concordance index and calibration evaluated by calibration plot, a plot of observed proportions versus predicted probabilities. Bootstrapping technique was used to adjust for over-fitting and over-optimistic model performance. The area under the curve (AUC) were compared using the nonparametric approach of DeLong et al.¹⁹ All experiments performed were endorsed by the Ethics Committee of Southern Medical University and complied with the Declaration of Helsinki. All statistical analyses were performed using R software version 3.5.1 with additional functions. All p values were calculated by two-sided statistical tests, unless notified otherwise.

Results

Demographic characteristic

Participants' characteristics were analyzed based on the original dataset without imputation. Baseline characteristics outlining those who developed intracranial infection versus those who did not were presented in table 1. Among the 380 participants, 209 (55%) were confirmed with

intracranial infection. Overall, the mean age of the participants was 38.16 ± 17.47 years, and 63.64% were male.

Count of patients meeting the diagnostic criteria:

- (1) CSF bacterial cultures or second-generation sequencing were positive: 188 patients.
- (2) CSF Gram stain and cultures were positive: 32 patients.
- (3) a. CSF WBC count $\geq 1000/\mu\text{L}$ and the WBC count of CSF increased in the second time;
- b. CSF below 2.5 mmol/L or a ratio of CSF to blood glucose < 0.4 : 85 patients.

Number of participants with missing data for each variable of interest

The percentage of deletions in our study was: multinuclear percentage, 2.8% CSF lactate concentration, 8.1% CSF Cl⁻, 2.9%, CSF glucose 3%, CSF ADA 2.6%, CSF total protein 2.9%, blood glucose 3.6%, procalcitonin 28.4%, and the CSF/Blood glucose ratio 5.2%.

Candidate variables for consideration

CSF WBC count, CSF glucose concentration, CSF lactate concentration were incorporated into the nomogram for reaching statistical significance in the multivariate analysis ($p < 0.01$) and improving model's predictive ability. Age, sex, blood glucose concentration, serum procalcitonin, emergency surgery, procedures involving sinuses, duration of surgery previous antibiotic and CSF leak use were not identified as predictors, because they failed to reach statistical significance in the univariate analysis ($p > 0.01$). Although CSF multinuclear percentage, CSF Cl⁻, CSF ADA, CSF total protein, CSF/Blood glucose ratio and serum CRP reach statistical significance in the univariate analysis ($p < 0.01$), they weren't incorporated into the nomogram. That is because they

cannot improve the prediction performance of the nomogram.

Nomogram development

In Table 1, all the variables obtained before patients' getting infected were included in the univariable analysis. Predictors that were significant at $P<0.01$ in univariable analysis were considered for multivariable regression with backward elimination. This procedure was conducted in the five imputed dataset separately. Variables that were significant in the five imputed dataset were included to develop the nomogram. After combining the results across the imputed datasets by Rubin's rules, we identified CSF WBC count, CSF lactate concentration, and CSF glucose concentration as independent predictors of infection which were incorporated into the Nomogram (Table 2; Fig. 1).

This nomogram achieved a concordance index of 0.933 (95%CI: 0.903-0.956) for infection prediction (Fig. 1). The receiver operating characteristics curves (ROCs) of models with CSF WBC counts, CSF glucose or CSF lactate and the nomogram are shown in Fig. 2. The calibration plots show the close agreement between predicted and observed risk of intracranial infection, with no apparent overprediction or underprediction (Fig.3).

Compare the nomogram with single variables

We then compared the discriminative power of the nomogram with single variables incorporated in the nomogram. The combined concordance index of the nomogram from the five imputed datasets was 0.933(95%CI:0.903-0.956, significantly larger than that of CSF WBC counts, CSF lactate, CSF glucose by Delong's test, of which concordance indexes were 0.888 (95%CI:0.851-

0.918), 0.839 (95% CI: 0.798-0.874), 0.776 (95% CI: 0.731-0.817), respectively (Supplemental Table 1).

Outcome

There were significantly different in duration of antibiotic therapy time and treatment failure between the use of the nomogram for predicting bacterial meningitis ($p=0.005$ and 0.041). Before the use of the nomogram for predicting bacterial meningitis, the duration of antibiotic therapy time is 21.1(7-41) days, after the use of the nomogram the duration of antibiotic therapy time is 17.34 (8-21) days. Before the use of the nomogram the treatment failure rate is 18.7%, after the use of the nomogram the treatment failure rate is 5.3% (Table 3)

Risk Score Development

A nomogram is a simple graphical representation of a statistical predictive model that creates a numerical probability of a clinical event. We have constructed a nomogram for predicting PNBM based on results of multivariable logistic regression analysis of age, sex, blood glucose, serum procalcitonin, CSF multinuclear percentage, CSF Cl⁻, CSF ADA, CSF total protein and the CSF/Blood glucose ratio. There were three significant predictors of PNBM incorporated into the nomogram. These predictors included CSF WBC count, CSF glucose, and CSF lactate, which were significant influencing factors that predicted PNBM. CSF lactate can be produced by bacterial metabolism.²⁷ CSF lactate level was significantly high in bacterial than viral meningitis.²⁸ In this study, we found that CSF lactate is one of the primary predictors of PNBM.

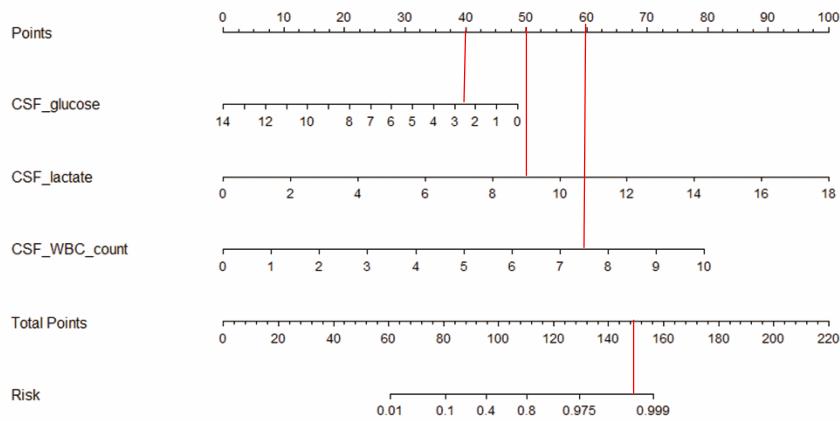
Sensitivity Analysis

We then validated its accuracy externally in an patient cohort. The statistic and calibration plot were used to assess the discrimination and calibration of the risk model. The result showed that the nomogram for predicting PNBM is able to accurately predict intracranial infection. The risk model demonstrated good discriminative power (optimism-corrected C statistic of 0.933). In addition, the calibration plots of our nomogram indicated that the model presented here was well-calibrated. Therefore, this nomogram provides a simple and convenient tool for use by clinicians to predict PNBM.

performance of our nomogram

We also applied decision curve analysis to measure the performance of our nomogram (Figure 4). It was used to evaluate the potential clinical application of the nomogram by quantifying the net benefits. The nomogram demonstrated high potential of clinical application compared with CSF glucose, CSF lactate and CSF WBC count.

How to use Nomogram ?



Eg: WBC counts: $7.5 \times 10^9/L$ CSF glucose: 2.5mmol/L CSF lactate concentration 9mmol/L
 Total point : 150 points (40+50+60)

Risk :0.993

Discussion

PNBM is an infectious disease of the central nervous system (CNS) characterized by high mortality and morbidity.^{20,21} Postoperative CSF leakage, skull base surgical approaches, placement of implants, duration of the operation, and postoperative drain can increase the chance of infection after neurosurgery.²² Accurate and rapid diagnosis of PNBM is important, since the infection outcome will depend on early and specific antibiotic therapy.²³ The clinical characteristics of bacterial meningitis include fever, headache, meningitis and altered mental state.^{6, 10, 11}

Cerebrospinal fluid (CSF) culture remains the golden standard for the diagnosis of PNBM. But the percent positive results are only about 10%.²⁴ And it takes a long time to get results. CSF or blood parameter has been able to discriminate between PNBM and nonbacterial meningitis (NBM). However, several studies have demonstrated the limited values of cerebrospinal fluid biochemical

parameters because of low sensitivity and specificity.^{25, 26} In addition, many factors will affect the diagnostic accuracy of pnbm, such as subjective differences between doctors, repeatability and specificity, and standardization. It may be more accurate to predict the PNBM with multiple results. Identifying early PNBM can help clinician to treat the bacterial meningitis better and save lives. Considering all these influencing factors, Based on the study, we have constructed and validated a nomogram that is able to predict the PNBM. The nomogram prediction model only uses the basic parameters of cerebrospinal fluid to improve the diagnostic sensitivity and positive / negative predictive value of bacterial meningitis, and it is cheap. Moreover, it is a visual graph, which makes the results of the prediction model more readable, convenient for patient evaluation, and can quickly, intuitively and quantitatively analyze the risk incidence, To provide more diagnostic decisions and evaluate the efficacy of antibiotics.

Duration of treatment

So far, there is still no stopping standard of antibiotics for pnbm. In the context of Neurosurgery, individual prediction of meningitis remains a challenge. In the past, the duration of our antibiotic treatment was mainly based on the recommendations of routine guidelines for meningitis, rather than evidence. When there are no pathogenic results, the duration of antibiotic treatment is often difficult. Since the nomogram chart was developed, when risk < 0.05, we believe that the risk of meningitis is a small probability event. Therefore, according to risk = 0.05, as the risk limit for stopping the use of antibiotics, the duration of antibiotics is shortened and treatment failure rate is reduced.

Imaging of patients with suspected PNM

We usually have to go through CT scanning 24 hours and 72 hours after operation, mainly to check whether there is bleeding, hydrocephalus, tumor resection, peripheral brain edema, intracranial effusion and gas accumulation in the operation area, which has no obvious specificity compared with the imaging examination of meningitis for patients in the early stage after neurosurgery. For the patients with negative cerebrospinal fluid culture, Mr (T1, T2, DWI) scanning was performed for these patients with suspected postoperative intracranial infection, and some possible evidences were found, such as whole brain edema, hydrocephalus, epidural empyema, subdural empyema, In order to determine the entrance of infection into the central nervous system, high-resolution thin-layer computed tomography with bone window will be an acceptable imaging method. In most centers, neuroimaging is routinely performed as part of the initial examination of suspected PNM and other post neurosurgical infections. It is unclear whether all patients suspected of infection after neurosurgery need this routine general imaging.

4

Limitations of This Study

Although nomogram has many advantages, it also has some limitations. Because there are many missing variables in the validation database, on the basis of ensuring the efficiency of the model, we use as few variable parameters as possible to enter the model. Retrospective studies have limitations and specific risk of bias, so prospective cohort was used for internal validation to reduce these bias. In this study, only a nomogram based on single center cases is established, and the generalization of nomogram to other cohorts with similar characteristics still needs to be verified. Our findings have yet to be confirmed by other independent studies. Whether the model predicts

BM in the special case of pnbm rather than in other cases remains to be solved. This study is a single center study, and the universality of risk score to other populations still needs to be verified. In addition, the bootstrap program that estimates over optimism is based on the developed risk score, which does not include the model selection step. In this case, there may be a large deviation from the overly optimistic estimate.

Conclusion

Developing an easy tool to predict risk of intracranial infection in postoperative neurosurgical patients within a short time is crucial for intracranial infection's early therapy. We have developed a nomogram that is able to predict this event, which can assist clinicians to plan and initiate the most appropriate disease management for patients in time.

Funding

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Declarations of interests

The authors declare no conflict of interest.

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Figure legend:

Figure 1. Nomogram for predicting intracranial infection based on the data obtained before infection.

Figure 2. Receiver operator characteristic curves showing area under the curve for intracranial infection patients. Receiver operator characteristic curves showing area under the curve for CSF white blood cell counts, 0.888; CSF lactate, 0.839; CSF glucose, 0.776; Nomogram, 0.933.

Figure 3. Calibration curve for predicting infection rate using the developed nomogram of developing dataset and validation dataset

Figure 4. Comparison of the predictive accuracies of diagnostic models among nomogram and white blood cell counts, CSF glucose, and CSF lactate concentration by decision curve analysis (DCA). The y-axis measures the net benefits.

Table 1. Characteristics for Included Patients

Variable	Non-infection (n=171)	Infection (n=209)	<i>P</i>
Age (year)	37.5(18.1)	38.7(17.0)	0.513
Sex (%)			
Male	100 (58.5)	133(63.6)	0.196
Female	71(41.5)	76(36.3)	
CSF WBC count x10^9 /µL	50.0(13.0-204.0)	1117.5(360.0-2340.5)	<0.001
CSF Multinuclear percentage (%)	70.0(55.0-80.0)	80.0(70.0-90.0)	<0.001
CSF lactate mmol/L	2.6(2.1-3.4)	5.3(4.2-7.2)	<0.001
CSF Cl ⁻ mmol/L	122.58(8.6)	119.76(8.2)	0.001
CSF glucose mmol/L	4.0(1.5)	2.6(1.6)	<0.001
CSF ADA mmol/L	0.6(0.2-1.3)	2.1(1.2-3.7)	<0.001
Total protein mmol/L	0.7(0.4-1.4)	1.6(1.0-2.7)	<0.001
Blood glucose mmol/L	5.6(4.6-7.7)	5.8(4.9-7.7)	0.183
Procalcitonin mmol/L	0.2(0.1-0.58)	0.2(0.1-0.6)	0.459
The ratio of CSF to blood glucose	0.6(0.5-0.8)	0.4(0.3-0.5)	<0.001
Emergency surgery	12(7.0)	21(10.0)	0.297
Procedures involving sinuses	10(5.8)	15(7.2)	0.603
Duration of surgery	231.6(65.3-612.2)	233.9(70.1-643.2)	0.239
Previous antibiotic use	160(93.6%)	200 (95.7%)	0.356
CSF leak	6(3.5)	9(4.3)	0.691
Serum CRP	49.7(20.3-92.6)	58.4(21.3-94.1)	<0.001
Whole brain edema	12(7%)	26(12.4%)	0.080
Subdural abscess	0(0%)	4(1.9%)	0.000
Epidural abscess	0(0%)	5(2.4%)	0.000
Hydrocephalus	11(6.4%)	25(11.5%)	0.067

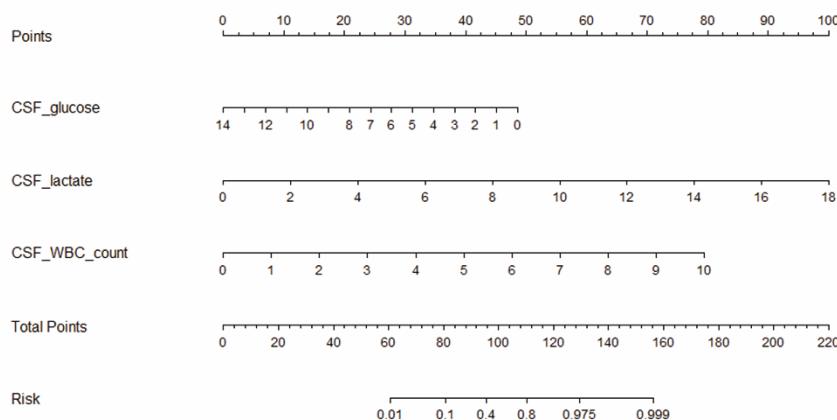
Table 2. Univariable and Multivariable Logistic Regression Analysis of Candidate Risk Factors for infection

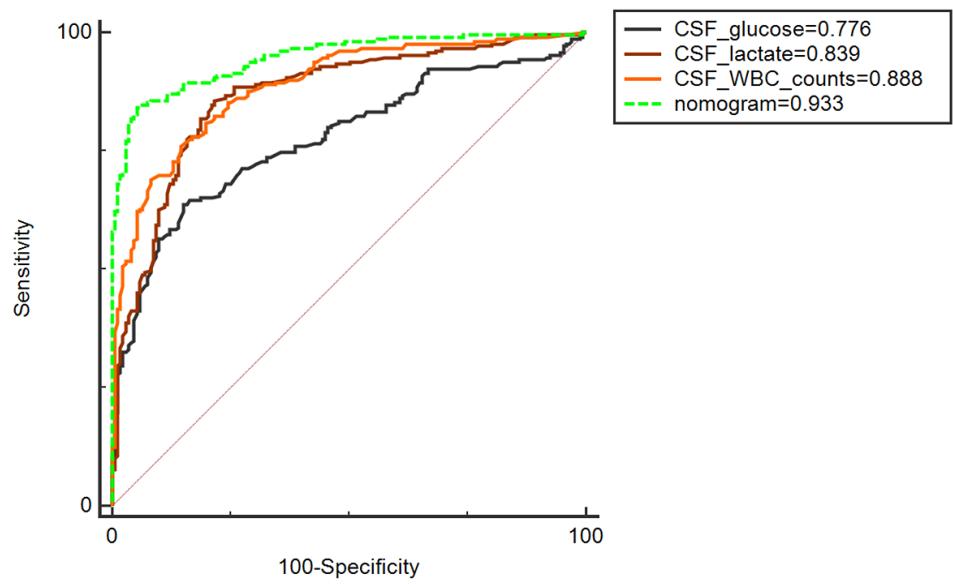
Variable	Univariable analysis		Multivariable analysis		
	OR(95%CI)	P	Coefficient	OR(95%CI)	P
Age	1.00(1.00-1.03)	0.511			
Sex, male	0.81(0.53-1.25)	0.355			
CSF WBC count	2.80(2.27-3.45)	<0.001	0.906	2.47(1.92-3.19)	<0.001
Multinuclear percentage			<0.001		
	1.02(1.00-1.04)				
CSF lactate	2.26(1.90-2.69)	<0.001	0.626	1.87(1.55-2.26)	<0.001
CSF Cl ⁻	0.95(0.93-0.98)	0.02			
CSF glucose	0.51(0.43-0.61)	<0.001	-0.433	0.65(0.52-0.82)	<0.001
CSF ADA	2.01(1.56-2.45)	<0.001			
Total protein	1.03(0.95-1.11)	<0.001			
Blood glucose	1.21(0.70-2.11)	0.152			
Procalcitonin	1.24(0.60-1.49)	0.09			
The ratio of CSF to blood glucose	0.35(0.20-0.61)	<0.001			
Emergency surgery	1.17(0.65-1.35)	0.252			
Procedures involving sinuses	2.04(1.62-2.25)	0.611			
Duration of surgery	1.21(0.74-1.48)	0.216			
Previous antibiotic use	0.98(0.39-1.16)	0.521			
CSF leak	1.03(0.71-1.19)	0.375			

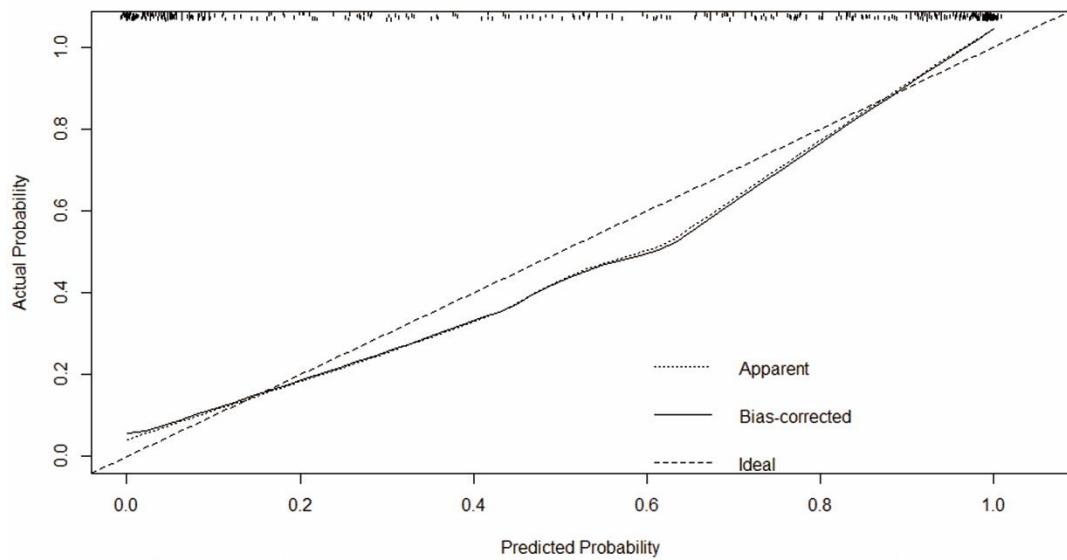
Serum CRP	0.31(0.19-0.59)	<0.001
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Table 3. Outcome Before and after use of the nomogram for predicting bacterial meningitis

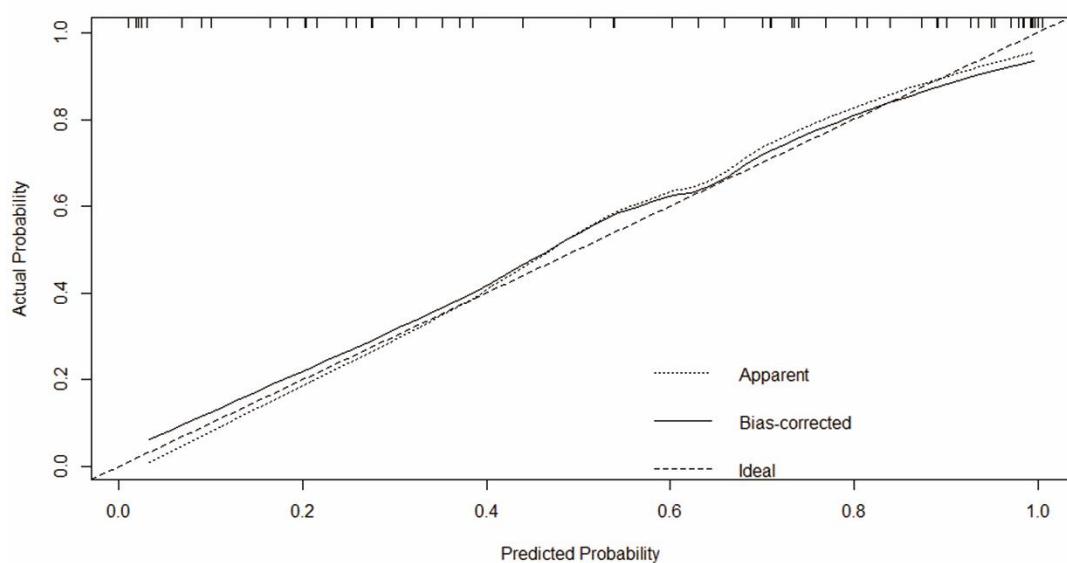
Variable	Before (n=209)	After (n=38)	P
Duration of antibiotic therapy	21.12(7-41)	17.34(8-21)	0.005
Treatment failure	39(18.7)	2(5.3)	0.041





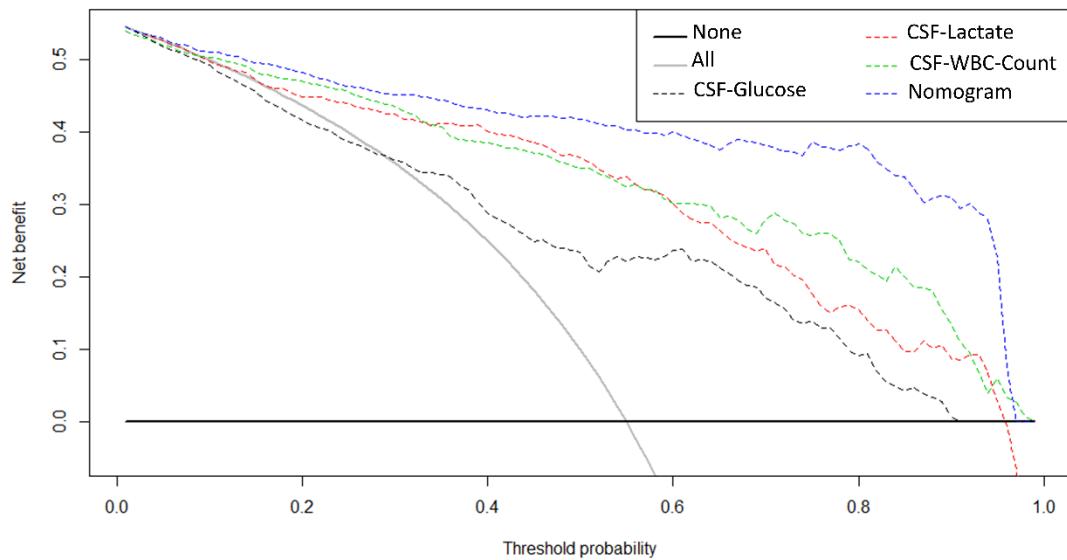


A



B

Figure 3.



Supplemental Table 1. C-index for single variable and the developed nomogram in the imputed dataset

	CSF count C-index(95%CI)	WBC C- index(95%CI)	CSF lactate C- index(95%CI)	CSF glucose C- index(95%CI)	Nomogram C- index(95%CI)
Imputed dataset 1	0.888(0.851-0.918)	0.868(0.829-0.900)	0.776(0.731-0.817)	0.947(0.919-0.967)	
Imputed dataset 2	0.888(0.851-0.918)	0.811(0.768-0.849)	0.776(0.731-0.817)	0.927(0.896-0.951)	
Imputed dataset 3	0.888(0.851-0.918)	0.815(0.772-0.853)	0.776(0.731-0.817)	0.921(0.889-0.946)	
Imputed dataset 4	0.888(0.851-0.918)	0.863(0.824-0.896)	0.775(0.730-0.816)	0.936(0.907-0.959)	
Imputed dataset 5	0.888(0.851-0.918)	0.838(0.797-0.873)	0.775(0.730-0.816)	0.932(0.902-0.955)	
Combined	0.888(0.851-0.918)	0.839(0.798-0.874)	0.776(0.731-0.817)	0.933(0.903-0.956)	

Table S1: STROBE Statement—Checklist of items to include when reporting observational studies

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title and Abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found.	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
objectives	3	State specific objectives, including any prespecified hypotheses.	5
Methods			
Study design	4	Present key elements of study design early in the paper.	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	--
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	7
Bias	9	Describe any efforts to address potential sources of bias.	7
Study size	10	Explain how the study size was arrived at.	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4-5
		(b) Describe any methods used to examine subgroups and interactions	5

		(c) Explain how missing data were addressed (d) Cohort study—If applicable, explain how loss to follow-up was addressed. Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	4 -- --
		(e) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9 8 -
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Cohort study—Summarise follow-up time (eg, average and total amount)	9 9 -
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time Case-control study—Report numbers in each exposure category, or summary measures of exposure Cross-sectional study—Report numbers of outcome events or summary measures	- -- --
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10 10 --
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

* Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

--: Not applicable.

Table S2: TRIPOD statement—Checklist of items to include when reporting a study developing or validating a multivariable prediction model for diagnosis or prognosis*

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5-6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6
	5c	D;V	Give details of treatments received, if relevant.	--
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	--
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	--
Sample size	8	D;V	Explain how the study size was arrived at.	7
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8
	10c	V	For validation, describe how the predictions were calculated.	--
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	9
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	--

Risk groups	11	D;V	Provide details on how risk groups were created, if done.	5
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	--
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	9
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	9
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	--
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	10
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	10
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	11
	15b	D	Explain how to use the prediction model.	12
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	12
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	--
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	15
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	15
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	15
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	15
Other information				
Supplemental information	21	D;V	Provide information about the availability of Supplemental resources, such as study protocol, Web calculator, and data sets.	25-29
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	16

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD explanation and elaboration document.

--: Not applicable.



Development and validation of a nomogram for predicting bacterial meningitis in postoperative neurosurgical patients

Authors:

Qiang Wu^{1,2}, MD; Yun Bao¹, MD, PhD; Haorun Huang¹, MD; Bing-Hui Qiu¹, MD; An Zhang¹, MD; Ming Jin³, MD; Yi-Ping Mo¹, MD; Ya-Wei Liu¹, PhD; Song-Tao Qi¹, MD, PhD; Fen Mei¹, PhD

Affiliations:

¹Department of Neurosurgery, Nanfang Hospital, Southern Medical University, Guangzhou, China

²Department of Neurosurgery, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region, China

³ Department of Gastroenterology, Shenzhen Hospital, Southern Medical University, Shenzhen, China

Qiang Wu, Yun Bao and Binghui Qiu contributed equally to this manuscript.

Corresponding Author:

Songtao Qi, MD, PhD and Fen Mei, PhD, Department of Neurosurgery, NanFang Hospital, Southern Medical University, Guangzhou Dadao Bei Street 1838#, Guangzhou, China

Tel/Fax: +86-20-61641801

E-mails: qisongtaonfy@126.com (Qi), meifen813@126.com(Mei)

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Qiang Wu, Yun Bao, Binghui Qiu performed primary data analysis and wrote the manuscript.

Qiang Wu, An Zhang, Haorun Huang, Ming Jin and Yi-Ping are responsible for the collection of date. Ya-Wei Liu and Yun Bao performed statistical analysis of the data. Songtao Qi, Fen Mei designed and supervised the study. All authors edited and approved the final manuscript.

Abstract

Background: The purpose of this analysis was to create a nomogram for predicting postneurosurgical bacterial meningitis.

Method: A retrospective study of patients underwent neurosurgical operation and clinically suspected postneurosurgical bacterial meningitis admitted to neurosurgical intensive care unit of Nanfang Hospital, Southern medical University from 15 January 2014 to 15 January 2020. Firstly, the model was internally validated using bootstrap resampling. Subsequently, it was externally validated in a separate cohort of patients (N=63) from 16 January 2020 to 16 January 2021. The concordance index and calibration curve was used to assess the discrimination and calibration of the model. Decision analysis curve was used to evaluate the clinical performance.

Results: Independent factors derived from multivariable analysis of the primary cohort to predict intracranial infection were CSF WBC count (cerebrospinal fluid white blood cell count), CSF lactate concentration, and CSF glucose concentration. They were all assembled into a nomogram to predict intracranial infection. The calibration curve for predicting the probability of intracranial infection showed that the nomogram-based predictions were in good agreement with actual observations. The C-index (concordance index) of nomogram model for risk prediction of intracranial infection was 0.933 (compared with only CSF glucose, CSF lactate, CSF WBC counts, $P < 0.001$, DeLong's test). The results were confirmed in the validation cohort (C-index =0.908). Decision analysis curve demonstrated that the nomogram is a valuable tool.

Conclusion: The proposed nomogram may be served as an effective tool for predicting post-neurosurgical bacterial meningitis.

Trial registration: Medical Ethics Committee of Nanfang Hospital(Seal), NFEC-2018-050 ,

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Key Words:

neurosurgical patients; bacterial meningitis; predicting; nomogram

Introduction

Postneurosurgical bacterial meningitis (PNBM) in neurosurgical patients is a common and serious postoperative complication that threatens patients' lives after neurosurgery¹⁻³, with a mortality of 20 to 50%⁴⁻⁷. Furthermore, survivors of bacterial meningitis have a high risk of cognitive impairment or other neurological deficits⁸. The most common causes of bacterial meningitis are: craniotomy for head trauma, brain tumor or intracranial hemorrhage, placement of external ventricular device, placement of ventriculoperitoneal shunt and ventriculostomy⁹. Patients usually present with fever, vomiting, meningeal irritation, and altered consciousness^{6, 10, 11}. PNBM requires immediate medical treatment. Early treatment with antibiotics reduces mortality in patients with PNBM, and therefore, rapid diagnosis is necessary¹²⁻¹⁴. The early diagnosis of PNBM is often difficult^{11, 13, 15}. Cerebrospinal fluid can be tested for the diagnosis of PNBM¹⁵. The CSF sample is examined for white blood cell count, red blood cell count, protein content, glucose level and bacterial culture. Diagnosis of PNBM should not be made on a single abnormal result, because a single test result may not be reliable in the early phase of the disease¹⁶. It may be more accurate to predict the PNBM with multiple results. The present study was performed to evaluate the prediction effect of the nomogram for predicting PNBM.

Methods

Study Population and Database

A retrospective observational study was conducted. The primary cohort comprised 380 postoperative neurosurgical patients, aged 16 to 77 years old from 15 January 2014 to 15 January

2020, in Nanfang Hospital, Southern Medical University. From 16 January 2020 to 16 January 2021, an independent cohort of postoperative neurosurgical patients (N=63) was prospectively enrolled at the same institution for validation. Both the primary and independent cohort used the same inclusion and exclusion criteria. All participants had given informed consent for this specific study.

Samples of CSF were collected from postoperative neurosurgical patients with suspected bacterial meningitis to develop the nomogram for early prediction of PNBM. Patients had at least one clinical manifestation of bacterial meningitis including fever (temperature \geq 38.5 °C), vomiting, meningeal irritation and altered consciousness. The values of CSF and blood samples were collected during first 8h after the clinical manifestation of bacterial meningitis appeared. CSF analysis included: gram stain and culture, white and red blood cell counts, multinuclear percentage, as well as protein concentration, glucose concentration, Cl⁻, adenosine deaminase (ADA), lactate concentration and the CSF/Blood glucose ratio. Blood analysis included: glucose, procalcitonin (PCT) and C-reactive protein (CRP). Clinical parameters examined included: age, sex, types of surgical procedure.

Primary End Point

The primary end point was the diagnosis of bacterial meningitis according to Practice Guidelines for the Management of Bacterial Meningitis⁹. PNBM confirmed on accurate diagnostic criteria which is (1) CSF ~~bacterial cultures or~~ second-generation sequencing were positive, (2) CSF Gram stain and cultures were positive, (3) a. CSF WBC count \geq 1000/ μ L and the WBC count of

CSF increased in the second time; b. CSF below 2.5 mmol/L or a ratio of CSF to blood glucose < 0.4.

Sample Size and Missing Data

We had used the rule of thumb recommended by Peduzzi¹⁷ and Harrell¹⁸, events per variable (EPV) being 10 or greater under this circumstance. We considered about 5 significant clinical factors in developing model. This would have required us to recruit at least 50 patients to have meningitis (the event) out of the total cohort to allow 5 independent variables into the model.a minimum of 50 (5×10) participants who had event prediction for the development of infection.

The percentage of deletions in our study was: multinuclear percentage, 2.8% CSF lactate concentration, 8.1% CSF Cl⁻, 2.9%,CSF glucose 3%, CSF ADA2.6%, CSF total protein 2.9%, blood glucose 3.6% , procalcitonin 28.4%, and the CSF/Blood glucose ratio5.2%

For missing data in this study, we assumed missing data occurred at random depending on the clinical variables and conducted multiple imputations. The fully conditional specification (FCS) regression method with 5 imputations was used to impute continuous variables. All analyses were performed based on imputed complete cases.

Statistical analysis:

Comparisons between normally distributed continuous variables, expressed as mean ± SD, were performed using two sample t-test. Non-normally distributed continuous variables, presented as median and interquartile range, were analyzed using Wilcoxon rank-sum tests. For categorical data, expressed as percentages, the Pearson chi-square or Fisher exact tests were used, as appropriate. We used multiple imputation to impute missing values for multinuclear percentage,

CSF lactate concentration, CSF Cl⁻, CSF glucose, CSF ADA, CSF total protein, blood glucose, procalcitonin, and the CSF/Blood glucose ratio which were used in the main analyses. We carried out five imputations. Univariable and multivariable analyses were conducted to develop the nomogram. Candidate predictors that were significant at P<0.01 in univariable analysis and were of biological interest or clinical importance were considered for multivariable regression.

Backward elimination was used to identify the variables associated with the development of meningitis risk factor for developing the nomogram. The coefficients for each variables risk factor were estimated in the five imputed datasets. Besides, Rubin's rule was used to combine the results across the imputed datasets. The interaction of predictors' clinical significance was also examined.

The predictive accuracy of the nomogram was assessed by both discrimination measured by concordance index and calibration evaluated by calibration plot, a plot of observed proportions versus predicted probabilities. Bootstrapping technique was used to adjust for over-fitting and over-optimistic model performance. The area under the curve (AUC) were compared using the nonparametric approach of DeLong et al.¹⁹ All experiments performed were endorsed by the Ethics Committee of Southern Medical University and complied with the Declaration of Helsinki. All statistical analyses were performed using R software version 3.5.1 with additional functions. All p values were calculated by two-sided statistical tests, unless notified otherwise.

Results

Demographic characteristic

Participants' characteristics were analyzed based on the original dataset without imputation. Baseline characteristics outlining those who developed intracranial infection versus those who did not were presented in table 1. Among the 380 participants, 209 (55%) were confirmed with intracranial infection. Overall, the mean age of the participants was 38.16 ± 17.47 years, and 63.64% were male.

Count of patients meeting the diagnostic criteria:

- (1) CSF bacterial cultures or second-generation sequencing were positive: 188 patients.
- (2) CSF Gram stain and cultures were positive: 32 patients.
- (3) a. CSF WBC count $\geq 1000/\mu\text{L}$ and the WBC count of CSF increased in the second time;
- b. CSF below 2.5 mmol/L or a ratio of CSF to blood glucose < 0.4 : 85 patients.

Number of participants with missing data for each variable of interest

The percentage of deletions in our study was: multinuclear percentage, 2.8% CSF lactate concentration, 8.1% CSF Cl⁻, 2.9%, CSF glucose 3%, CSF ADA 2.6%, CSF total protein 2.9%, blood glucose 3.6%, procalcitonin 28.4%, and the CSF/Blood glucose ratio 5.2%.

Candidate variables for consideration

CSF WBC count, CSF glucose concentration, CSF lactate concentration were incorporated into the nomogram for reaching statistical significance in the multivariate analysis ($p < 0.01$) and improving model's predictive ability. Age, sex, blood glucose concentration, serum procalcitonin, emergency surgery, procedures involving sinuses, duration of surgery previous antibiotic and CSF leak use were not identified as predictors, because they failed to reach statistical significance

in the univariate analysis ($p>0.01$). Although CSF multinuclear percentage, CSF Cl⁻, CSF ADA, CSF total protein, CSF/Blood glucose ratio and serum CRP reach statistical significance in the univariate analysis ($p<0.01$), they weren't incorporated into the nomogram. That is because they cannot improve the prediction performance of the nomogram.

Nomogram development

In Table 1, all the variables obtained before patients' getting infected were included in the univariable analysis. Predictors that were significant at $P<0.01$ in univariable analysis were considered for multivariable regression with backward elimination. This procedure was conducted in the five imputed dataset separately. Variables that were significant in the five imputed dataset were included to develop the nomogram. After combining the results across the imputed datasets by Rubin's rules, we identified CSF WBC count, CSF lactate concentration, and CSF glucose concentration as independent predictors of infection which were incorporated into the Nomogram (Table 2; Fig. 1).

This nomogram achieved a concordance index of 0.933 (95%CI: 0.903-0.956) for infection prediction (Fig. 1). The receiver operating characteristics curves (ROCs) of models with CSF WBC counts, CSF glucose or CSF lactate and the nomogram are shown in Fig. 2. The calibration plots show the close agreement between predicted and observed risk of intracranial infection, with no apparent overprediction or underprediction (Fig.3).

Compare the nomogram with single variables

We then compared the discriminative power of the nomogram with single variables incorporated

in the nomogram. The combined concordance index of the nomogram from the five imputed datasets was 0.933(95%CI:0.903-0.956, significantly larger than that of CSF WBC counts, CSF lactate, CSF glucose by Delong's test, of which concordance indexes were 0.888 (95%CI:0.851-0.918), 0.839 (95% CI: 0.798-0.874), 0.776 (95% CI: 0.731-0.817), respectively (Supplemental Table 1).

Outcome

There were significantly different in duration of antibiotic therapy time and treatment failure between the use of the nomogram for predicting bacterial meningitis ($p=0.005$ and 0.041). Before the use of the nomogram for predicting bacterial meningitis, the duration of antibiotic therapy time is 21.1(7-41) days, after the use of the nomogram the duration of antibiotic therapy time is 17.34 (8-21) days. Before the use of the nomogram the treatment failure rate is 18.7%, after the use of the nomogram the treatment failure rate is 5.3% (Table 3)

Risk Score Development

A nomogram is a simple graphical representation of a statistical predictive model that creates a numerical probability of a clinical event. We have constructed a nomogram for predicting PNBM based on results of multivariable logistic regression analysis of age, sex, blood glucose, serum procalcitonin, CSF multinuclear percentage, CSF Cl⁻, CSF ADA, CSF total protein and the CSF/Blood glucose ratio. There were three significant predictors of PNBM incorporated into the nomogram. These predictors included CSF WBC count, CSF glucose, and CSF lactate, which were significant influencing factors that predicted PNBM. CSF lactate can be produced by bacterial

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metabolism.²⁷ CSF lactate level was significantly high in bacterial than viral meningitis.²⁸ In this study, we found that CSF lactate is one of the primary predictors of PNBM.

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Sensitivity Analysis

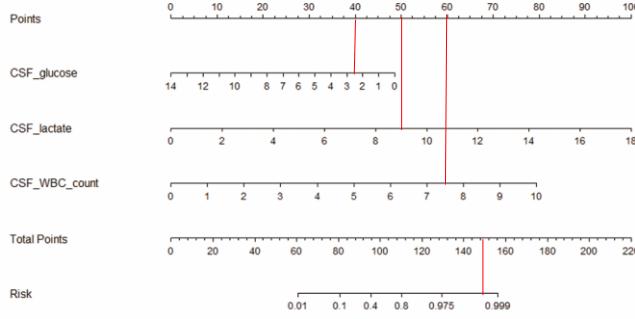
We then validated its accuracy externally in an patient cohort. The statistic and calibration plot were used to assess the discrimination and calibration of the risk model. The result showed that the nomogram for predicting PNBM is able to accurately predict intracranial infection. The risk model demonstrated good discriminative power (optimism-corrected C statistic of 0.933). In addition, the calibration plots of our nomogram indicated that the model presented here was well-calibrated. Therefore, this nomogram provides a simple and convenient tool for use by clinicians to predict PNBM.

performance of our nomogram

We also applied decision curve analysis to measure the performance of our nomogram (Figure 4). It was used to evaluate the potential clinical application of the nomogram by quantifying the net benefits. The nomogram demonstrated high potential of clinical application compared with CSF glucose, CSF lactate and CSF WBC count.

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How to use Nomogram ?



Eg: WBC counts: $7.5 \times 10^9/L$ CSF glucose: 2.5mmol/L CSF lactate concentration 9mmol/L

Total point : 150 points (40+50+60)

Risk :0.993

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Discussion

PNBM is an infectious disease of the central nervous system (CNS) characterized by high mortality and morbidity.^{20,21} Postoperative CSF leakage, skull base surgical approaches, placement of implants, duration of the operation, and postoperative drain can increase the chance of infection after neurosurgery.²² Accurate and rapid diagnosis of PNBM is important, since the infection outcome will depend on early and specific antibiotic therapy.²³ The clinical characteristics of bacterial meningitis include fever, headache, meningitis and altered mental state.^{6, 10, 11} Cerebrospinal fluid (CSF) culture remains the golden standard for the diagnosis of PNBM. But the percent positive results are only about 10%.²⁴ And it takes a long time to get results. CSF or blood parameter has been able to discriminate between PNBM and nonbacterial meningitis (NBM). However, several studies have demonstrated the limited values of cerebrospinal fluid biochemical

parameters because of low sensitivity and specificity.^{25, 26} In addition, many factors will affect the diagnostic accuracy of pnbm, such as subjective differences between doctors, repeatability and specificity, and standardization. It may be more accurate to predict the PNBM with multiple results. Identifying early PNBM can help clinician to treat the bacterial meningitis better and save lives. Considering all these influencing factors,-Based on the study, we have constructed and validated a nomogram that is able to predict the PNBM.-The nomogram prediction model only uses the basic parameters of cerebrospinal fluid to improve the diagnostic sensitivity and positive / negative predictive value of bacterial meningitis, and it is cheap. Moreover, it is a visual graph, which makes the results of the prediction model more readable, convenient for patient evaluation, and can quickly, intuitively and quantitatively analyze the risk incidence. To provide more diagnostic decisions and evaluate the efficacy of antibiotics.

Duration of treatment

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So far, there is still no stopping standard of antibiotics for pnbm. In the context of Neurosurgery, individual prediction of meningitis remains a challenge. In the past, the duration of our antibiotic treatment was mainly based on the recommendations of routine guidelines for meningitis, rather than evidence. When there are no pathogenic results, the duration of antibiotic treatment is often difficult. Since the nomogram chart was developed, when risk < 0.05, we believe that the risk of meningitis is a small probability event. Therefore, according to risk = 0.05, as the risk limit for stopping the use of antibiotics, the duration of antibiotics is shortened and treatment failure rate is reduced.

Imaging of patients with suspected PNM

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We usually have to go through CT scanning 24 hours and 72 hours after operation, mainly to check whether there is bleeding, hydrocephalus, tumor resection, peripheral brain edema, intracranial effusion and gas accumulation in the operation area, which has no obvious specificity compared with the imaging examination of meningitis for patients in the early stage after neurosurgery. For the patients with negative cerebrospinal fluid culture, Mr (T1, T2, DWI) scanning was performed for these patients with suspected postoperative intracranial infection, and some possible evidences were found, such as whole brain edema, hydrocephalus, epidural empyema, subdural empyema. In order to determine the entrance of infection into the central nervous system, high-resolution thin-layer computed tomography with bone window will be an acceptable imaging method. In most centers, neuroimaging is routinely performed as part of the initial examination of suspected PNM and other post neurosurgical infections. It is unclear whether all patients suspected of infection after neurosurgery need this routine general imaging.

A nomogram is a simple graphical representation of a statistical predictive model that creates a numerical probability of a clinical event. We have constructed a nomogram for predicting PNBM based on results of multivariable logistic regression analysis of age, sex, blood glucose, serum procalcitonin, CSF multinuclear percentage, CSF Cl⁻, CSF ADA, CSF total protein and the CSF/Blood glucose ratio. There were three significant predictors of PNBM incorporated into the nomogram. These predictors included CSF WBC count, CSF glucose, and CSF lactate, which were significant influencing factors that predicted PNBM. CSF lactate can be produced by bacterial metabolism.²⁷ CSF lactate level was significantly high in bacterial than viral meningitis.²⁸ In this study, we found that CSF lactate is one of the primary predictors of PNBM.

We then validated its accuracy externally in an patient cohort. The statistic and calibration plot were used to assess the discrimination and calibration of the risk model. The result showed that the nomogram for predicting PNBM is able to accurately predict intracranial infection. The risk model demonstrated good discriminative power (optimism-corrected C statistic of 0.933). In addition, the calibration plots of our nomogram indicated that the model presented here was well-calibrated. Therefore, this nomogram provides a simple and convenient tool for use by clinicians to predict PNBM.

We also applied decision curve analysis to measure the performance of our nomogram (Figure 4). It was used to evaluate the potential clinical application of the nomogram by quantifying the net benefits. The nomogram demonstrated high potential of clinical application compared with CSF glucose, CSF lactate and CSF WBC count.⁴

Limitations of This Study

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Although nomogram has many advantages, it also has some limitations. Because there are many missing variables in the validation database, on the basis of ensuring the efficiency of the model, we use as few variable parameters as possible to enter the model. Retrospective studies have limitations and specific risk of bias, so prospective cohort was used for internal validation to reduce these bias. In this study, only a nomogram based on single center cases is established, and the generalization of nomogram to other cohorts with similar characteristics still needs to be verified. Our findings have yet to be confirmed by other independent studies. Whether the model predicts BM in the special case of pnbm rather than in other cases remains to be solved. This study is a

single center study, and the universality of risk score to other populations still needs to be verified.
In addition, the bootstrap program that estimates over optimism is based on the developed risk
score, which does not include the model selection step. In this case, there may be a large deviation
from the overly optimistic estimate.

Conclusion

Developing an easy tool to predict risk of intracranial infection in postoperative neurosurgical patients within a short time is crucial for intracranial infection's early therapy. We have developed a nomogram that is able to predict this event, which can assist clinicians to plan and initiate the most appropriate disease management for patients in time.

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Declarations of interests

The authors declare no conflict of interest.

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Figure legend:

Figure 1. Nomogram for predicting intracranial infection based on the data obtained before infection.

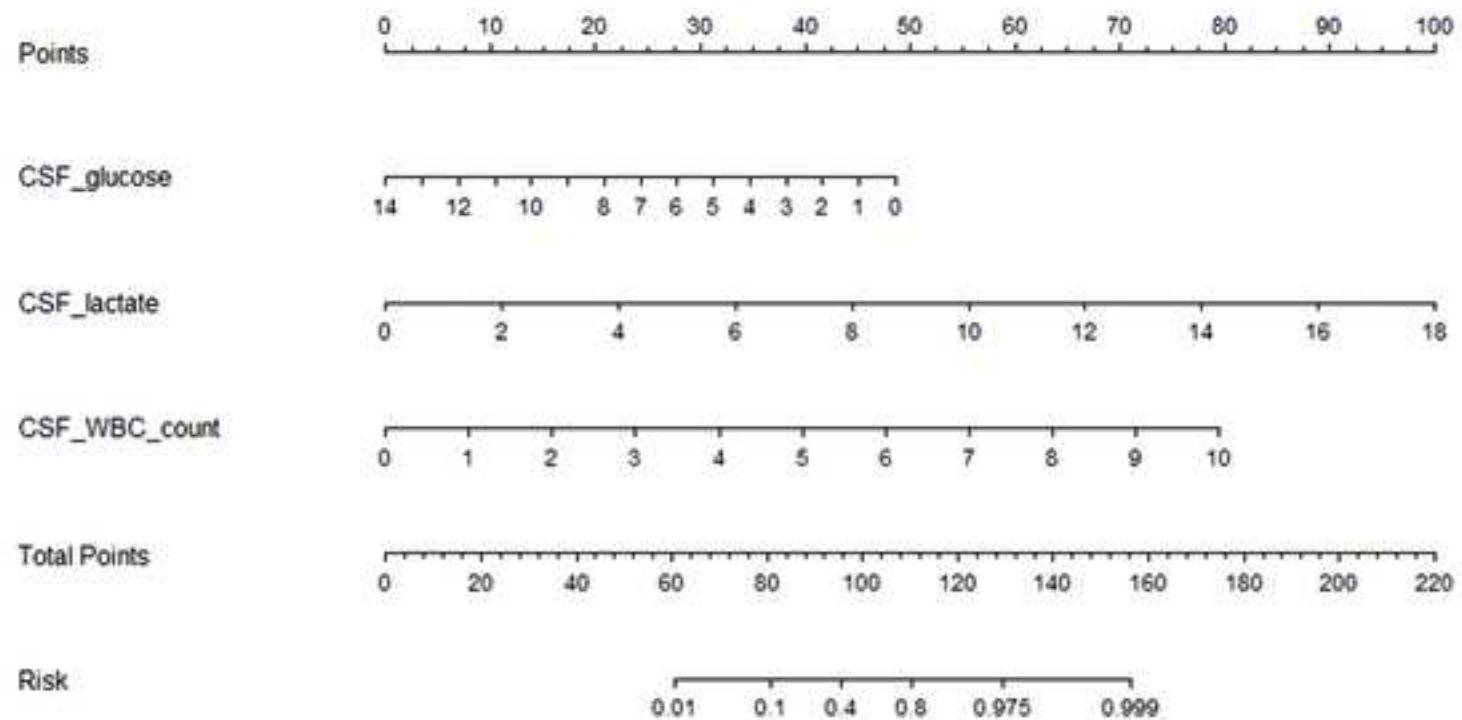
Figure 2. Receiver operator characteristic curves showing area under the curve for intracranial infection patients. Receiver operator characteristic curves showing area under the curve for CSF white blood cell counts, 0.888; CSF lactate, 0.839; CSF glucose, 0.776; Nomogram, 0.933.

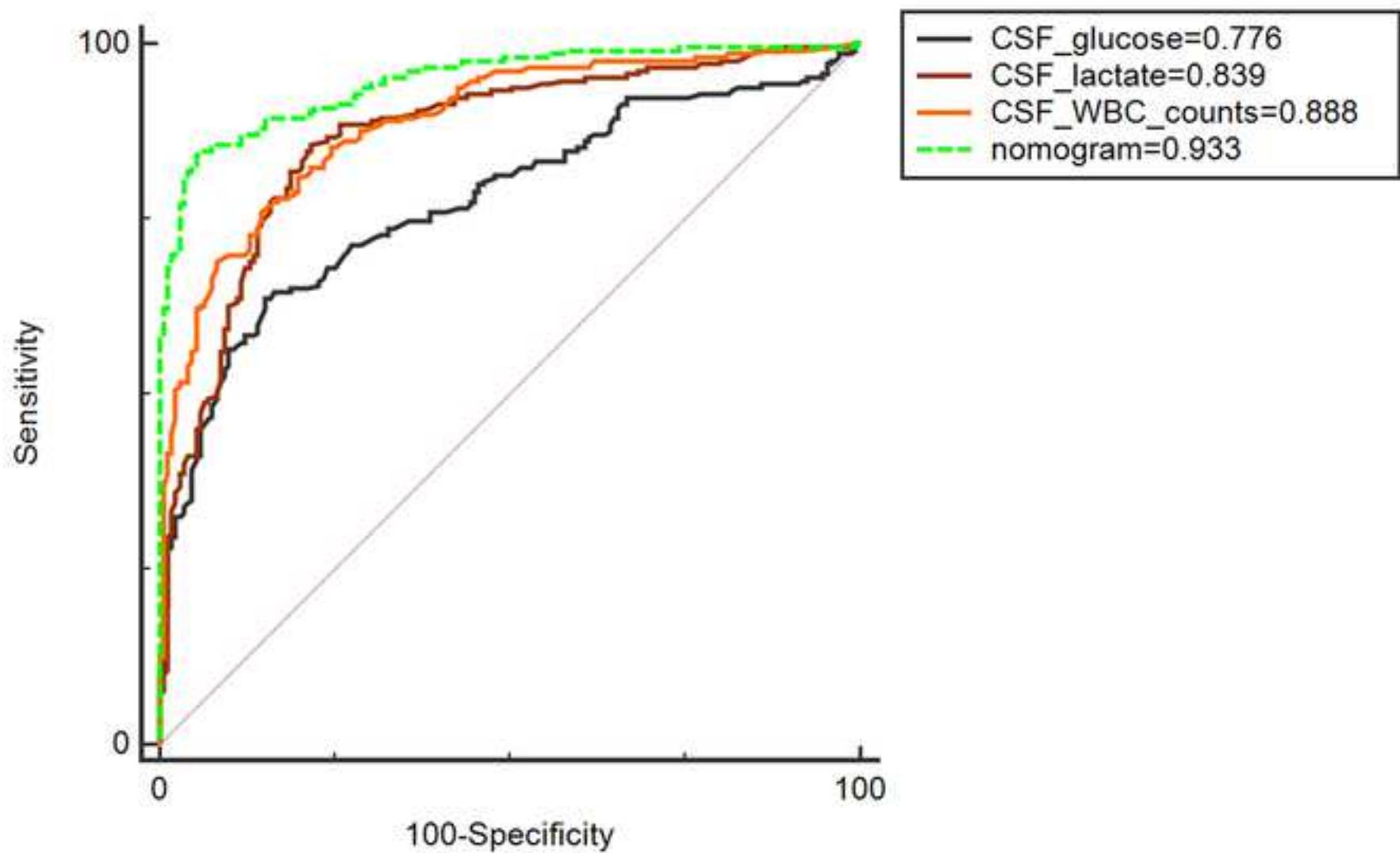
Figure 3. Calibration curve for predicting infection rate using the developed nomogram of developing dataset and validation dataset

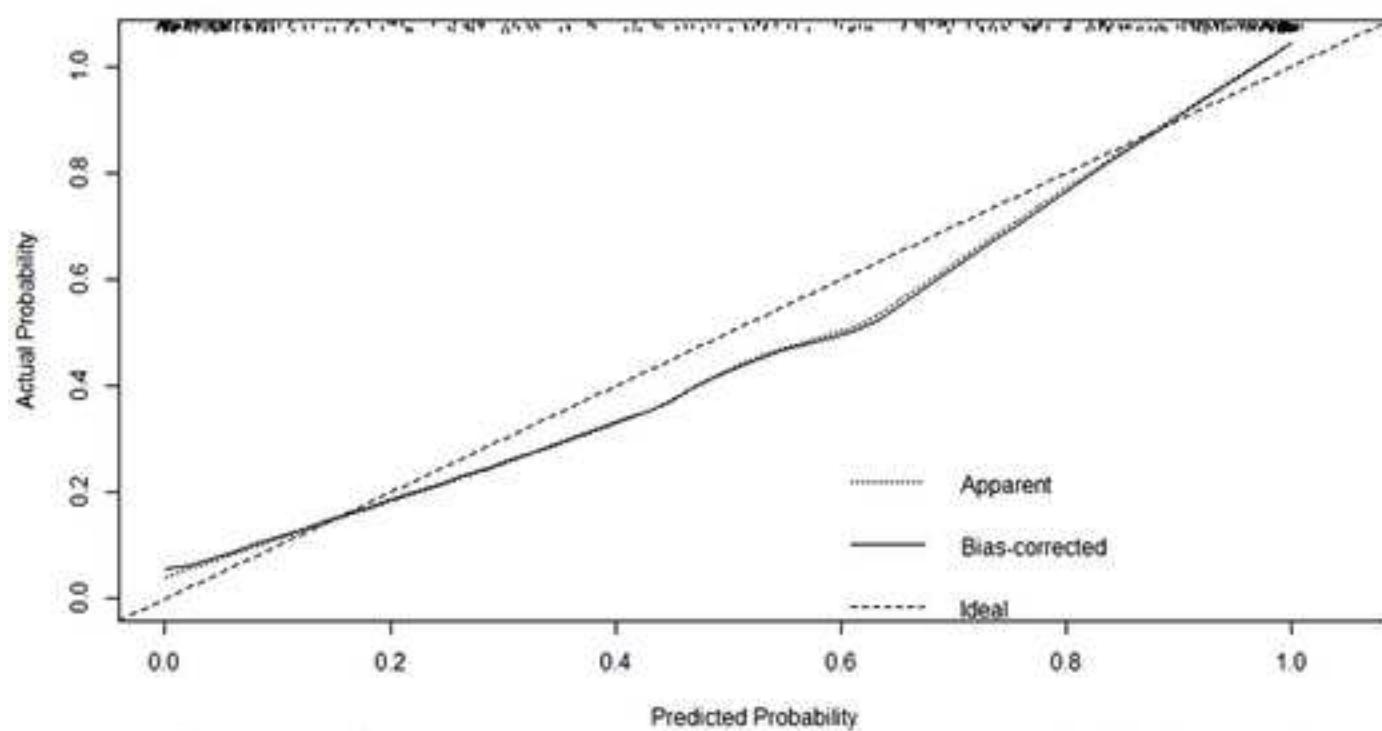
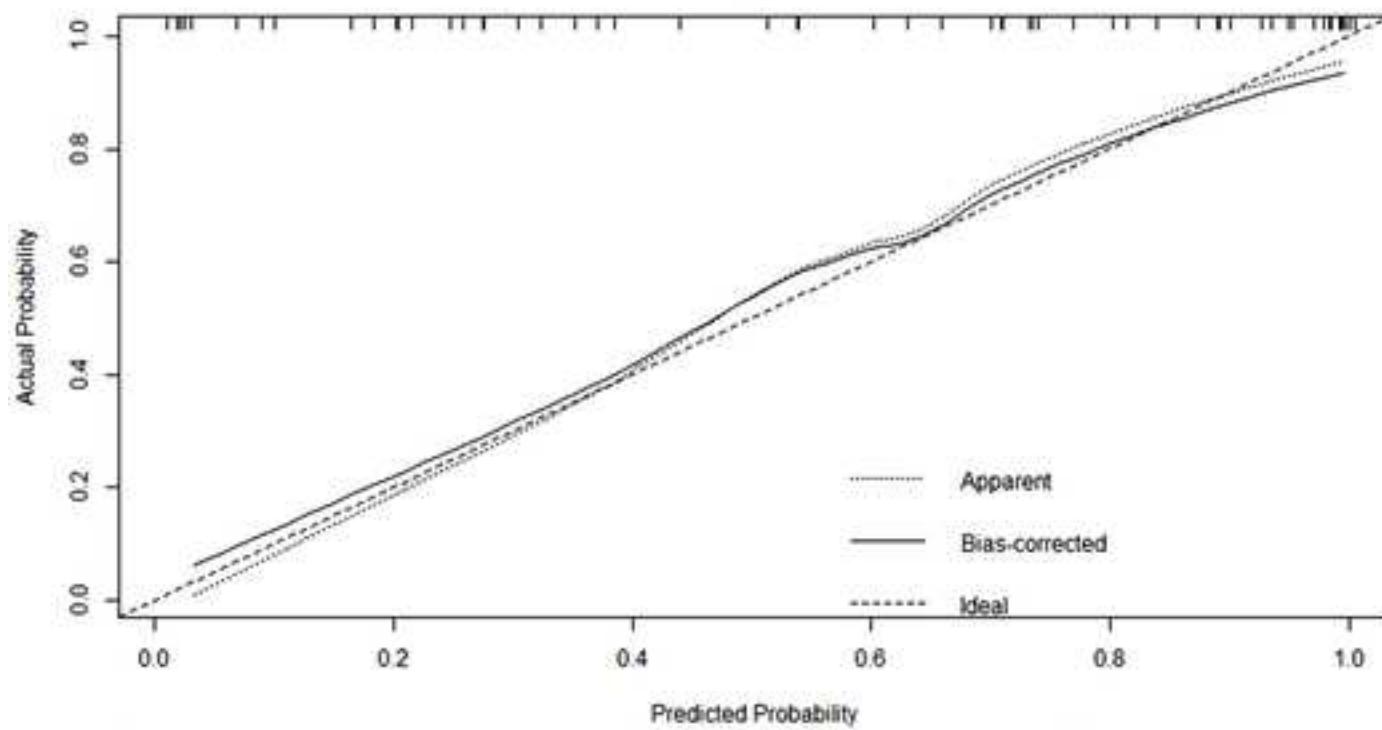
Figure 4. Comparison of the predictive accuracies of diagnostic models among nomogram and white blood cell counts, CSF glucose, and CSF lactate concentration by decision curve analysis (DCA). The y-axis measures the net benefits.

Variable	Non-infection (n=171)	Infection (n=209)	P
Age (year)	37.5(18.1)	38.7(17.0)	0.513
Sex (%)			
Male	100 (58.5)	133(63.6)	0.196
Female	71(41.5)	76(36.3)	
CSF WBC count x10 ⁹ /µL	50.0(13.0-204.0)	1117.5(360.0-2340.5)	<0.001

CSF Multinuclear percentage (%)	70.0(55.0-80.0)	80.0(70.0-90.0)	<0.001
CSF lactate mmol/L	2.6(2.1-3.4)	5.3(4.2-7.2)	<0.001
CSF Cl ⁻ mmol/L	122.58(8.6)	119.76(8.2)	0.001
CSF glucose mmol/L	4.0(1.5)	2.6(1.6)	<0.001
CSF ADA mmol/L	0.6(0.2-1.3)	2.1(1.2-3.7)	<0.001
Total protein mmol/L	0.7(0.4-1.4)	1.6(1.0-2.7)	<0.001
Blood glucose mmol/L	5.6(4.6-7.7)	5.8(4.9-7.7)	0.183
Procalcitonin mmol/L	0.2(0.1-0.58)	0.2(0.1-0.6)	0.459
The ratio of CSF to blood glucose	0.6(0.5-0.8)	0.4(0.3-0.5)	<0.001
Emergency surgery	12(7.0)	21(10.0)	0.297
Procedures involving sinuses	10(5.8)	15(7.2)	0.603
Duration of surgery	231.6(65.3-612.2)	233.9(70.1-643.2)	0.239
Previous antibiotic use	160(93.6%)	200 (95.7%)	0.356
CSF leak	6(3.5)	9(4.3)	0.691
Serum CRP	49.7(20.3-92.6)	58.4(21.3-94.1)	<0.001
<u>Whole brain edema</u>	<u>12(7%)</u>	<u>26(12.4%)</u>	<u>0.080</u>
<u>Subdural abscess</u>	<u>0(0%)</u>	<u>4(1.9%)</u>	<u>0.000</u>
<u>Epidural abscess</u>	<u>0(0%)</u>	<u>5(2.4%)</u>	<u>0.000</u>
<u>Hydrocephalus</u>	<u>11(6.4%)</u>	<u>25(11.5%)</u>	<u>0.067</u>





**A****B**

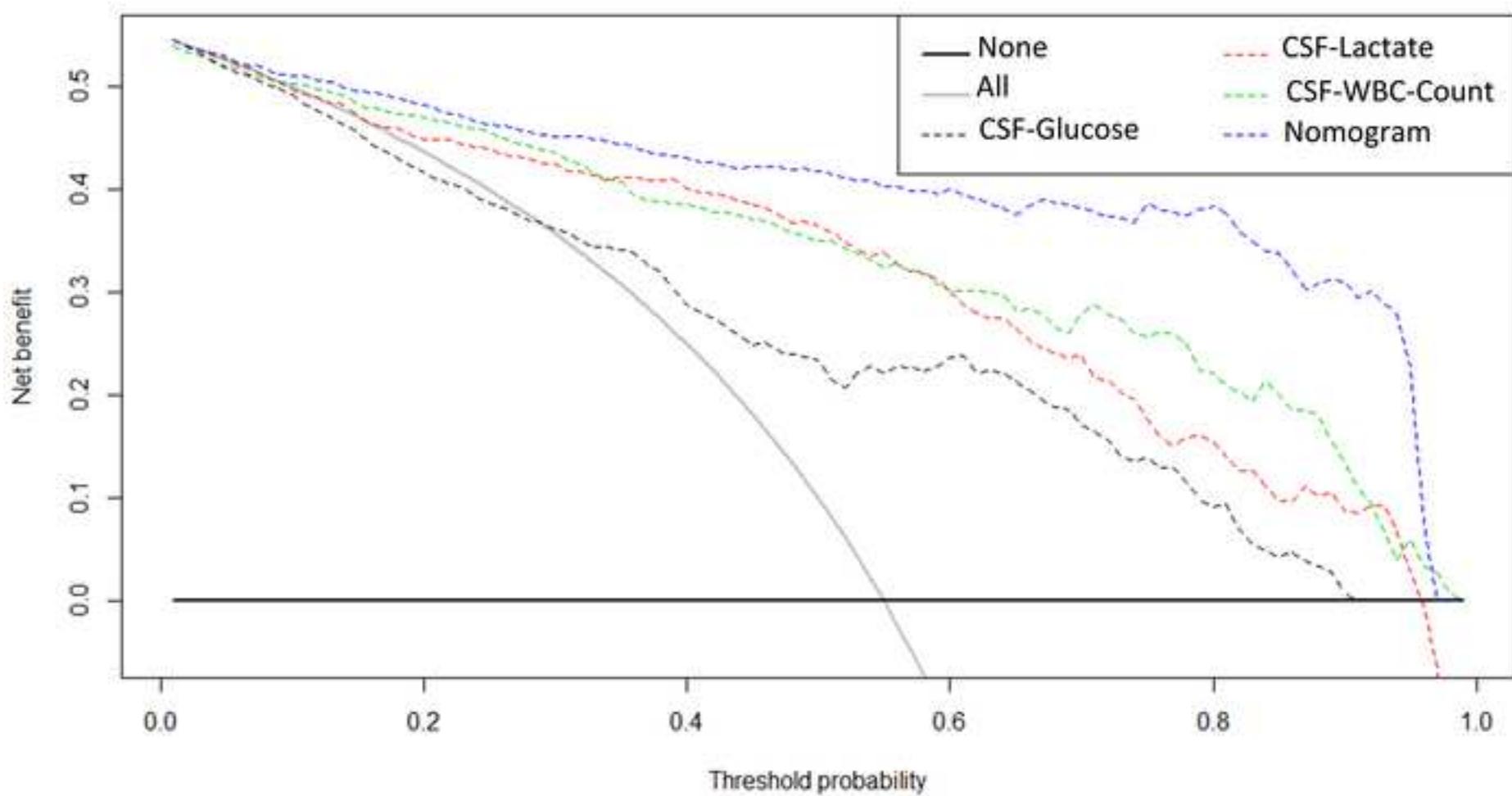


Table 1. Characteristics for Included Patients

Variable	Non-infection (n=171)	Infection (n=209)	P
Age (year)	37.5(18.1)	38.7(17.0)	0.513
Sex (%)			
Male	100 (58.5)	133(63.6)	0.196
Female	71(41.5)	76(36.3)	
CSF WBC count x10^9 /µL	50.0(13.0-204.0)	1117.5(360.0-2340.5)	<0.001
CSF Multinuclear percentage (%)	70.0(55.0-80.0)	80.0(70.0-90.0)	<0.001
CSF lactate mmol/L	2.6(2.1-3.4)	5.3(4.2-7.2)	<0.001
CSF Cl ⁻ mmol/L	122.58(8.6)	119.76(8.2)	0.001
CSF glucose mmol/L	4.0(1.5)	2.6(1.6)	<0.001
CSF ADA mmol/L	0.6(0.2-1.3)	2.1(1.2-3.7)	<0.001
Total protein mmol/L	0.7(0.4-1.4)	1.6(1.0-2.7)	<0.001
Blood glucose mmol/L	5.6(4.6-7.7)	5.8(4.9-7.7)	0.183
Procalcitonin mmol/L	0.2(0.1-0.58)	0.2(0.1-0.6)	0.459
The ratio of CSF to blood glucose	0.6(0.5-0.8)	0.4(0.3-0.5)	<0.001
Emergency surgery	12(7.0)	21(10.0)	0.297
Procedures involving sinuses	10(5.8)	15(7.2)	0.603
Duration of surgery	231.6(65.3-612.2)	233.9(70.1-643.2)	0.239
Previous antibiotic use	160(93.6%)	200 (95.7%)	0.356
CSF leak	6(3.5)	9(4.3)	0.691
Serum CRP	49.7(20.3-92.6)	58.4(21.3-94.1)	<0.001
Whole brain edema	12(7%)	26(12.4%)	0.080
Subdural abscess	0(0%)	4(1.9%)	0.000
Epidural abscess	0(0%)	5(2.4%)	0.000
Hydrocephalus	11(6.4%)	25(11.5%)	0.067

Table 2. Univariable and Multivariable Logistic Regression Analysis of Candidate Risk Factors for infection

Variable	Univariable analysis		Multivariable analysis		
	OR(95%CI)	P	Coefficient	OR(95%CI)	P
Age	1.00(1.00-1.03)	0.511			
Sex, male	0.81(0.53-1.25)	0.355			
CSF WBC count	2.80(2.27-3.45)	<0.001	0.906	2.47(1.92-3.19)	<0.001
Multinuclear percentage	1.02(1.00-1.04)	<0.001			
CSF lactate	2.26(1.90-2.69)	<0.001	0.626	1.87(1.55-2.26)	<0.001
CSF Cl ⁻	0.95(0.93-0.98)	0.02			
CSF glucose	0.51(0.43-0.61)	<0.001	-0.433	0.65(0.52-0.82)	<0.001
CSF ADA	2.01(1.56-2.45)	<0.001			
Total protein	1.03(0.95-1.11)	<0.001			
Blood glucose	1.21(0.70-2.11)	0.152			
Procalcitonin	1.24(0.60-1.49)	0.09			
The ratio of CSF to blood glucose	0.35(0.20-0.61)	<0.001			
Emergency surgery	1.17(0.65-1.35)	0.252			
Procedures involving sinuses	2.04(1.62-2.25)	0.611			
Duration of surgery	1.21(0.74-1.48)	0.216			
Previous antibiotic use	0.98(0.39-1.16)	0.521			
CSF leak	1.03(0.71-1.19)	0.375			
Serum CRP	0.31(0.19-0.59)	<0.001			

Table 3. Outcome Before and after use of the nomogram for predicting bacterial meningitis

Variable	Before (n=209)	After (n=38)	P
Duration of antibiotic therapy	21.12(7-41)	17.34(8-21)	0.005
Treatment failure	39(18.7)	2(5.3)	0.041



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